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Is it too early to investigate survival outcomes of the new US heart allocation system?

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We read with interest the recent article by Cogswell et al.[1] on the new heart allocation system, which concluded that post-transplant survival had significantly decreased after implementation. We have concerns about the validity of this analysis. Specifically, it appears that the authors have overlooked the important non-informative censoring assumption of the Kaplan-Meier estimator.[2] This is more serious than the admitted limitation of wide confidence intervals around the estimates secondary to small sample size. Indeed, heavy informative censoring of the new system cohort may have biased the conclusion that post-transplant mortality is now significantly worse.

The authors constructed the new system Kaplan-Meier survival curve from 539 patients with only 32 deaths and 3 retransplants, a crude event rate of 6.5%. How then does the Kaplan–Meier survival estimator generate a 180-day mortality estimate of 22%? The explanation is the non-informative (random) censoring assumption, which is that censoring is not correlated with a patient's risk of death. This assumption is what allows for extrapolation of survival curves beyond the time the first patient is censored. The authors' analysis is overly reliant on this assumption. Although outcomes were "available up to June 6th, 2019" for new system recipients, the actual observed follow-up in this group was very short, with only 125 patients (23%) remaining at risk at 50 days and 45 (8%) remaining at 100 days. In contrast, the prior system cohort had a much lower rate of censoring, with 5,704 (95%) at risk at 50 days and 5,607 (93%) at risk at 100 days.

By performing survival analysis on this heavily censored data, the authors have increased the chance that their results are biased by informative censoring, which is when censored patients have a different survival experience than non-censored patients.[3] In the best case scenario sensitivity analysis in the supplement, the authors apply a 93.5% 180-day survival rate to the censored patients in the new system, increasing their estimate from 75% to 87% (Status 1–3 recipients). However, censored patients may have an even higher survival rate. In the post-transplant period, if patients are doing well, their follow-up is increasingly spaced out over time and therefore they are more likely to be censored by the study's truncated follow-up. In this case, censored patients have a lower risk of death than those not censored, violating the non-informative censoring assumption. If the sensitivity analysis is repeated

with the actual best case by assuming all censored patients survive to 180 days, the new system 6-month survival estimate is 93%.

We believe that the authors should have restricted their analysis to the first 30 days post-transplant before the vast majority of the censoring. In this follow-up period, there was no significant difference between the prior system and new system cohorts. Ultimately, once more follow-up data are available, Cogswell et al.'s conclusions may turn out to be valid. However, informative censoring may be inducing a significant bias into their analysis, and we recommend caution before concluding that the new system reduced post-transplant survival.

References

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